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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/040,206	01/02/2002	Vishwanath R. Lingappa	UCSF.002.01US	1150

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EXAMINER	
WINKLER, ULRIKE	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 04/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/040,206	LINGAPPA ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-14 and 51-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-14 and 51-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed October 6, 2003 in response to the Office Action of July 2, 2003 is acknowledged and has been entered. Claims 12-14 and 51-53 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Specification

Applicant is required to update the status (pending, allowed, ect.) of all parent priority applications in the first line of the specification.

The disclosure is objected to because of the following informalities: Example 12 is found on page 42 and on page 45, it appears that the example on page 45 should be number 13.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The rejection of claims 12-14 and 51-53 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **is maintained** for reasons of record.

Applicant's arguments have been fully considered but fail to persuade. Applicant's arguments are that the term refers to a protein which exists in two or more tertiary structures which also exhibit different function. Applicant makes reference to figure 14 as evidencing that there are two different conformational structures that are associated with HSP68. The

experiment uses an immunoprecipitation procedure in which a polyclonal antibody against HuHP68 was used to precipitate the HP68 complexes. Cells transfected with plasmid carrying Gag or BruΔenv were subjected to immunoprecipitation. The result that only Gag was precipitated HP68 was interpreted by Applicant's to mean that there are two conformational structures "conformers" for HP68. This interpretation is not convincing because (1) the HP68 may have a higher affinity for Gag and therefore the cellular pool of HP68 will associated with Gag when present in the cell (2) or alternatively that the presence of a plasmid or Gag in the cell may stimulate the cell to produce the RNase L inhibitor which then binds to RNase L displacing HP68 form the RNase L. Either scenario does not indicate that there are structural differences between HP68 when it associates with Gag or RNase L [see Martinand et al. RNase L inhibitor is induced during human immunodeficiency virus type 1 infection and down regulates the 2-5A?RNase L pathway in human T cells. Journal of Virology (Jan. 1999) Vol. 73, No. 1, pages 290-296; or Bisbal et al. Cloning and characterization of RNase L inhibitor. Journal of Biological Chemistry (1995) Vol. 270, No. 22, pages 13308-13317]. Therefore, term "conformer" renders the claims indefinite because the ordinary artisan would not know what is meant by this term. The specification has not provided a way to distinguish between the "conformers". Does "conformer" refer to the immature capsid in association with HP68 or does conformer refer to a mutant of HP68. The phrase "conformer" renders the claims indefinite because the specification does not provide a standard of measuring the degree intended by the term, thereby rendering the scope of the claim(s) unascertainable. See MPEP § 2173.05(f).

The rejection of claims 12-14 and 51-53 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention **is maintained** for reason of record.

Applicant's arguments have been fully considered but fail to persuade. Applicant's argument is that the methods of making a knock out mouse are well established in the art citing several references.

Neither the specification nor the prior art has provided any teaching regarding such a knockout animal, i.e. a mouse with a homozygous disruption of the gene encoding HP68. The specification has not disclosed any monoclonal antibodies produced by the methods as claimed. All transgenic models, whether targeted or untargeted, still may present unpredictable expression patterns due to incomplete knockout of the targeted gene, redundancy within the genome or unanticipated genetic interactions, such as down-regulation of other genes. (Taconic Newsletter, March 1996, Vol. 1, No. 2, page 4).

The claims encompass a genus of compounds (monoclonal antibodies) defined only by their function "binding to a conformer" without disclosing the structural differences between the "conformers". Applicant makes reference to figure 14 as evidencing that there are two different conformational structures that are associated with HSP68. The experiment uses an immunoprecipitation procedure in which a polyclonal antibody against HuHP68 was used to precipitate the HP68 complexes. Cells transfected with plasmid carrying Gag or BruΔenv were subjected to immunoprecipitation. The result that only Gag was precipitated HP68 was

interpreted by Applicant's to mean that there are two conformational structures "conformers" for HP68. This interpretation is not convincing because (1) the HP68 may have a higher affinity for Gag and therefore the cellular pool of HP68 will associated with Gag when present in the cell (2) or alternatively that the presence of a plasmid or Gag in the cell may stimulate the cell to produce the RNase L inhibitor which then binds to RNase L displacing HP68 form the RNase L. Either scenario does not indicate that there are structural differences between HP68 when it associates tithe Gag or RNase L [see Martinand et al. RNase L inhibitor is induced during human immunodeficiency virus type 1 infection and down regulates the 2-5A?RNase L pathway in human T cells. Journal of Virology (Jan. 1999) Vol. 73, No. 1, pages 290-296; or Bisbal et al. Cloning and characterization of RNase L inhibitor. Journal of Biological Chemistry (1995) Vol. 270, No. 22, pages 13308-13317]. The fact that one could have assayed/screened for a compound of interest using does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound would fall within the scope of what is claimed. In order to measure binding to a particular conformation structure would require that this tertiary structure is stable. Without such stability it would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity of binding a "conformer".

Claimed invention is drawn to an antibody identified by the method of claim 12. However, no structural or specific functional characteristics (specific epitope binding) of such an antibody is provided, nor is there any indication that the artisan actually implemented the method of claim 12 so as to identify any monoclonal antibodies. This situation is analogous to that of *Regents of the University of California v Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir.

1997). *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116.) Because one skilled in the art would conclude that the inventors were not in possession of the claimed invention. The claim fails to comply with the written description requirement.

The rejection of claims 12-14 and 51-53 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention **is maintained** for reasons of record.

Applicant's arguments have been fully considered but fail to persuade. Applicant's arguments are (1) that the methods of making a knock out mouse are well established in the art and (2) that the structure of the monoclonal antibody is not important per se but rather the three dimensional structure of the protein "conformer" used to generate the monoclonal antibody is significant.

Neither the specification nor the prior art has provided any teaching regarding a HP68 knockout animal. The specification also has not disclosed any monoclonal antibodies produced by the claimed method. All transgenic models, whether targeted or untargeted, still may present unpredictable expression patterns due to incomplete knockout of the targeted gene, redundancy

within the genome or unanticipated genetic interactions, such as down-regulation of other genes. (Taconic Newsletter, March 1996, Vol. 1, No. 2, page 4). Indicating that until an animal has actually been created there is a high degree of uncertainty. The claims as written do not appear to require germline transmission of the disrupted nucleotide sequence. It would be unpredictable if a disruption of a nucleotide sequence in a single cell would result in a phenotype (that would not have any HP68 protein in the animal); the instant specification has not provided any uses for a transgenic mouse that does not exhibit a phenotype resulting from disruption of a nucleotide sequence (see below). The claims encompasses transgenic mice that comprise a disruption in a host chaperone protein encoding gene, particularly the nucleotide sequence of HP68. Claims 12 embrace transgenic mice exhibiting a particular phenotype, wherein a broad interpretation of the claimed animals could read on disruption of a host chaperone protein encoding gene in a single cell. The specification has not taught that transgenic mouse embryos whose genomes comprise a homozygous disruption of the HP68 encoding gene and that these animals do not exhibit a phenotype of embryonic lethality. The state of the art at the time of filing was such that one of skill could not predict the phenotype of a knockout mouse (Moreadith et al. Gene targeting in embryonic stem cells: the new physiology and metabolism. Journal of Molecular Medicine (1997) Vol. 75, pages 208-216; see page 208, column 2, last full paragraph). Also see Leonard et al (Role of the common cytokine receptor gamma chain in cytokine signaling and lymphoid development. Immunological Reviews. (1995) No. 148, pages 97-114) who discuss that inactivation of the gene encoding cytokine receptor chain in transgenic mice results in a phenotype different from that expected. Finally, Moens et al. (Defects in heart and lung development in compound heterozygotes for two different targeted mutations at the N-myc

locus. Development (1993) Vol. 119, pages 485-499) disclose that two mutations produced by homologous recombination in two different locations of the N-myc gene produce two different phenotypes in mouse embryonic stem cells, one leaky and one null (see abstract). However, it would be difficult to predict any phenotype resulting from disruption of the sequence encoding HP68 in light of the above. Moreover, as the claims read on disruption of a host chaperone protein (HP68) protein encoding gene in a single cell, it would be unpredictable if such a disruption would result in any phenotype. The specification has not disclosed a transgenic mouse embryos whose genome comprises a homozygous disruption in the nucleotide sequence encoding the HP68 gene does not display embryonic lethality. Given the unpredictable nature of a phenotype that results from disruption of a nucleotide sequence it would have required undue experimentation for the skilled artisan to make and use the invention as claimed.

The claims encompass a genus of compounds (monoclonal antibodies) defined only by their function "binding to a conformer" without disclosing the structural differences between the "conformers". Applicant makes reference to figure 14 as evidencing that there are two different conformational structures that are associated with HSP68. The experiment uses an immunoprecipitation procedure in which a polyclonal antibody against HUHP68 was used to precipitate the HP68 complexes. Cells transfected with plasmid carrying Gag or BruΔenv were subjected to immunoprecipitation. The result that only Gag was precipitated HP68 was interpreted by Applicant's to mean that there are two conformational structures "conformers" for HP68. This interpretation is not convincing because (1) the HP68 may have a higher affinity for Gag and therefore the cellular pool of HP68 will associated with Gag when present in the cell (2) or alternatively that the presence of a plasmid or Gag in the cell may stimulate the cell to

produce the RNase L Inhibitor which then binds to RNase L which will then displace HP68 form the RNase L. Either scenario does not indicate that there are structural differences between HP68 when it associates tithe Gag or RNase L [see Martinand et al. RNase L inhibitor is induced during human immunodeficiency virus type 1 infection and down regulates the 2-5A?RNase L pathway in human T cells. Journal of Virology (Jan. 1999) Vol. 73, No. 1, pages 290-296; or Bisbal et al. Cloning and characterization of RNase L inhibitor. Journal of Biological Chemistry (1995) Vol. 270, No. 22, pages 13308-13317].

Making antibodies to a conformational structure is not a trivial matter and requires more than a mere road map on how applicants envision the production of this antibody. The generic procedure of immunizing a homozygous knockout animal with a protein having a stable conformational structure does not predictably result in an antibody that can recognize one "conformer" over the other "conformer" (see Prusiner et al. Ablation of the prion protein (PrP) gene in mice prevents scrapie and facilitates production of anti-PtP antibodies. Proceeding of the National Academy of Science (1993) Vol. 90, pages 10608-10612;). The lack of PrPC in PrP-p0/0 mice prevents them from becoming tolerant to the immunogen, the injection of the PrPSc infectious structure into the animal produced antibodies against PrP but these antibodies did not distinguish between the prion "conformers". "Surprisingly, given that we immunized mice with infectious Prp27-30 preparation, none of the rescued antibodies exclusively recognized this form of protein, whereas all but one antibody reacted well with a PrPC as it occurs on the cell surface" (see Williamson et al. Mapping the prion protein using recombinant antibodies. Journal of Virology (1998) Vol. 72, No. 11, pages 9413-9418, page 9417, column 1, 2nd paragraph).

The fact that one could have assayed/screened for a compound of interest using the claimed does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound would fall within the scope of what is claimed. In order to measure binding to a particular conformation structure it would require that this tertiary structure is stable. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity. The instant fact pattern fails to disclose that a monoclonal antibody has been produced using the claimed knockout animal. The specification does not provide any guidance or any working examples in this unpredictable art, and thus the artisan would have been unable to have prepared the claimed antibody without undue experimentation. Furthermore an assay for finding a product is not equivalent to a positive recitation of how to make such a product. This claim fails to meet the enablement requirement for the "how to make" prong of 35 U.S.C. § 112 first paragraph.

New Rejection:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

Claim 13 is rejected under 35 U.S.C. 102(b) as being anticipated by Willison et. al (Cell, 1989) as evidenced by applicants specification page 45 lines 25-27 indicating that the 23c antibody was used for the isolation of the WG68 conformer.

The instant invention is drawn to a monoclonal antibody that binds HP68. The recitation "conformational specificity for host chaperone protein that is involved in assembly of immature

HIV capsid and not to conformers of said host chaperone protein that do not bind Gag and do not facilitate HIV capsid assembly". has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Willison et al. discloses the production of a 23c hybridoma cell line producing a monoclonal anti-TCP-1alpha antibody, now available for purchase form Stressgen Biotechnologies (see table 1). This antibody was used by Applicant's to isolate the HP68 from wheat germ extracts, indicating that a known antibody structure bind HP68. Therefore, the instant invention drawn to monoclonal antibodies is anticipated by Willison et al.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 571-272-0902.

The official fax phone number for the organization where this application or proceeding is assigned is 703-872-9306; for informal communications please the fax phone number is 571-273-0912.

ULRIKE WINKLER, PHD.
PATENT EXAMINER 4/2/04